The components and properties of aqueous GI fluids to which a dosage form is exposed are important in determining the rate of dissolution and the level of solubilization, and therefore, the pattern of drug absorption. One important property of GI fluids is pH, which exerts a major influence on the overall absorption process for water-insoluble drugs since most drugs are either weak acids or bases and the drugs have to be in solution before being transported across the GI membrane. The pH of the fluids in the GI tract varies considerably, ranging from very acidic (pH 1) in the stomach to about neutral (pH 6–7) in the small intestine and somewhat basic (pH 8) in the large intestine. The aqueous solubility of acid and basic compounds and, by virtue of the Noyes–Whitney relationship, their dissolution rate from the dosage form is typically pH dependent. The pH of the fluids will have less impact for unionizable drugs. For example, acidic drugs dissolve most readily in alkaline media and, therefore, are expected to have a greater rate of dissolution in intestinal fluid than in gastric fluid. Furthermore, as the major site of drug absorption is the small intestine, it would seem that water-insoluble basic drugs need to dissolve in the acidic gastric fluids and to remain in solution in the intestinal environment to be well absorbed from the intestine. In some cases, however, the water-insoluble drug could be delivered through the unique formulation approaches and stayed as a stable solution or supersaturation form in the GI tract that lead to reasonable fraction absorbed and bioavailability.

Dissolution rate is a function of the drug concentration at the site of absorption, which is directly proportional to the saturation solubility of the drug. For a weakly acidic drug, increasing the pH increases the extent and rate at which the drug dissolves, which in turn can significantly influence the absorption behavior of the drug.

$$AH \overset{K_a}{\leftrightarrow} A^- + H^+$$

$$K_a = \frac{\left[A^-\right]\left[H^+\right]}{\left[AH\right]} \tag{22.1}$$

At a given pH, the saturation solubility of the drug in the boundary layer is

$$C_h = [AH] + [A^-] \tag{22.2}$$

When the drug is dissolving in an aqueous solution in which the drug is totally unionized, the drug saturation solubility is $C_s = [AH]$. Therefore,

$$C_h = C_s\left(1 + \frac{K_a}{\left[H^+\right]}\right) \tag{22.3}$$

For a weakly basic drug, however, the rate of dissolution decreases as the pH increases.

$$BH^+ \overset{K_b}{\leftrightarrow} B + H^+$$

$$K_b = \frac{\left[B\right]\left[H^+\right]}{\left[AH^+\right]} \tag{22.4}$$

Similarly, at a given pH

$$C_h = [BH^+] + [B] \tag{22.5}$$